Linking ’omic and Genetic Data to Physiologically Based Pharmacokinetic and Pharmacodynamic Modeling to Enhance Ecological and Human Health Risk Assessment

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A great deal of academic, private sector, and government research has been initiated to apply advanced molecular biological methods to the discovery of toxicity pathways in wildlife and humans. One aim is the prediction of health outcomes based on the combination of refined chemical structure analysis with mechanistic data from systems biology studies. Quantitative ecological and human health risk assessments are expected to improve significantly. However, up to now, much less investment has been made in understanding the molecular mechanisms underlying the distribution, metabolism, and eventual excretion of stressors (i.e., pharmacokinetics and dose metrics).

A collaborative project across the U.S. Environmental Protection Agency (U.S. EPA)/ORD is being developed to use ’omic (genomic, proteomic, and metabolomic) and genetic technologies to provide data that would be directly incorporated into physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models. The approach for this project integrates expertise across ecological and human health research sciences. Molecular as well as tissue-level and whole organism endpoints will be measured to reveal dose phenomena in model aquatic organisms, the water flea *Daphnia pulex* (invertebrate), and the zebrafish *Danio rerio* (vertebrate) to a prototypical chemical. These models have been and are presently the focus of considerable genome sequencing efforts that the U.S. EPA/ORD can use as a resource. In addition, genetic technologies (measurement of DNA sequence polymorphisms) will provide an opportunity to study the extent to which variation in pharmacologic parameters can be explained by genetics. The combination of all techniques will allow us to identify and compare novel dose- and time-dependent indicators across multiple biological and taxonomic levels while simultaneously critically evaluating the relevance and linkage of biological data generated from multiple experimental platforms. Integration of U.S. EPA/ORD bioinformatics capabilities with those of dose modelers has the potential to reduce the uncertainty in the exposure component of both ecological and human health risk assessments. Partnered with other researchers within the ORD’s Computational Toxicology Program, this project has the additional potential of forming linkages across a considerable portion of the source-to-outcome continuum that is within the purview of the U.S. EPA’s risk assessment mission.
Although this work was reviewed by the U.S. EPA and approved for publication, it may not

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